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Efficacy and Safety of Banhahubak-Tang for Depression Treatment: Study Protocol for a Randomized, Waitlist-Controlled Trial

Seung-Ho Lee[*,†,‡,#], **Yunna Kim**[*,†,‡,#], **Dohyung Kwon**[*,†,‡], **Seung-Hun Cho**[†,‡]

[*]Department of Clinical Korean Medicine, Graduate School, Kyung Hee University, [†]College of Korean Medicine, Kyung Hee University, [‡]Research Group of Neuroscience, East-West Medical Research Institute, WHO Collaborating Center, Kyung Hee University

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Correspondence to
Seung-Hun Cho
Kyung Hee University Medical Center, 23, Kyungheedae-ro, Dongdaemun-gu, Seoul, 02447, Korea.
Tel: +82-2-958-9186
Fax: +82-2-958-9187
E-mail: chosh@khmc.or.kr
[#]The first two authors contributed equally to this study.

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Objectives: Depression is a highly prevalent disease, and the market for antidepressant drugs continues to grow at a steady rate. Although current antidepressants are reported to be effective, because of their low remission rate and side effects, new antidepressants are needed. The use of Banhahubak-tang (BHT) to treat the symptoms of depression is supported by experimental evidence. The proposed study will evaluate the efficacy and safety of BHT in treating depression.

Methods: A randomized, waitlist-controlled, parallel clinical trial will be conducted to assess the efficacy of BHT in depression. A total of 84 participants with depression will be randomized into the intervention group or waitlist-control group at a 1:1 ratio. Patients in the intervention group will be administered BHT three times a day for four weeks and followed up for four more weeks after therapy completion. Patients in the waitlist-control group will undergo the same intervention and follow-up after a four-week waiting period. The primary outcome is change in the Korean version of the Hamilton Depression Rating Scale (K-HDRS) scores for major depressive disorders after four weeks. The secondary outcomes include scores on the K-HDRS, Korean Symptom Check List 95 (KSCL-95), Insomnia Severity Index (ISI), State-Trait Anxiety Inventory-Korean version (STAI-K), State-Trait Anger Expression Inventory-Korean version (STAXI-K), and the Instrument on Pattern Identifications for Depression and EuroQol-5 Dimension (EQ-5D).

Conclusions: This trial will provide high-quality clinical evidence of the efficacy and safety of BHT in the management of depression.

Key Words: Major depressive disorder, Banhahubak-tang, Herbal medicine, Randomized controlled trial, Protocol.

I. INTRODUCTION

Depression is a very common mental disorder that degrades the quality of life and causes functional impairments[1]. The main symptoms of depression are lethargy, decreased interest, appetite and sleep disorders, and suicidal ideation. In addition, concentration and memory may deteriorate, and chronic fatigue may occur. Physical symptoms, such as headache, indigestion, stiff neck and shoulders, and chest tightness, may also develop. In some cases, severe depression can cause psychotic symptoms such as delusions or hallucinations[2]. According to the World Health Organization (WHO), depression ranked 4th in disability-adjusted life year (DALY), defined as 'the number of years a person has lost a healthy life,' and was considered the second leading cause of disability in 2020. The antidepressant market is the third-largest drug market worldwide. The Korean domestic market was estimated to be worth about 122 million dollars in 2014, with the market size continuing to grow at a steady annual rate of 10~15%[3].

Selective serotonin reuptake inhibitors (SSRI) and tricyclic antidepressants (TCA) are the most commonly used antidepressants. Both drugs have an antidepressant effect but also limitations, such as a low remission rate and side effects. SSRIs' common side effects include nausea, vomiting, diarrhea, abdominal pain, burning sensation in the chest, and headache[4]. In the case of TCA, depersonalization, confusion, orthostatic hypotension, and severe sedation appear in the early stages and are known to cause blurred vision, severe dry mouth, weight gain, epilepsy, and extrapyramidal symptoms[5]. In addition, Asians are more than twice as likely to have poor CYP2C19 metabolism compared with Caucasian and African American so they are vulnerable to side effect or toxicity by TCA or SSRIs[6]. Therefore, there is a need for a new antidepressant suitable for Koreans, with fewer side effects. Therefore, interest in natural product-based therapeutics that are recognized for their safety and effectiveness for depression through long-term clinical experience is increasing[7].

BHT has been widely used in patients with digestive symptoms, dysphagia, cough, shortness of breath, throat discomfort, and vertigo in Korea, China, and Japan. The Ministry of Food and Drug Safety of the Republic of Korea also stipulates the indications for BHT to include anxiety neurosis, gastritis nervosa, cough, hoarseness, depressed mood, feeling a foreign body in the throat or esophagus, shortness of breath, dizziness, and nausea. BHT is composed of five medicinal herbs: Pinellia ternata, Machilus thunbergii, Wolfiporia extensa, Perilla frutescens var. crispa, and Zingiber officinale. Previous studies have reported that BHT is effective in animal models of chronic unpredicted mild stress (CUMS)-induced depression through several mechanisms, such as prohibiting NLR family pyrin domain containing 3 (NLRP3) inflammasome and IL-1β activation[8], improving the damage of brain-derived neurotrophic factor (BDNF) in the hippocampus and hypothalamus, and alleviating nerve atrophy[9]. A recent study estimated that the mitogen-activated protein kinase (MAPK) signaling pathway, epidermal growth factor (ErbB) signaling pathway, Hypoxia-inducible factor (HIF)-1 signaling pathway, and phosphoinositide 3-kinase (PI3K)-Akt pathway would be significant pathways, and found that BHT promotes mainly nerve growth and has anti-neuroinflammatory effects[10].

Despite this experimental evidence and approved indications, high-quality clinical evidence for major depressive disorder is lacking. Furthermore, only the antidepressant effect of a modified formula derived from BHT was reported in a retrospective controlled study[11]. Effects on other diseases accompanying depressive symptoms[12-14] have also been reported. Therefore, the present study aims to evaluate the ef-

ficacy and safety of BHT in depression through a randomized, waitlist-controlled trial.

II. METHODS

1. Study design

This is a randomized, waitlist-controlled, parallel-design trial to evaluate the safety and efficacy of BHT in patients with depression. Participants will be administered 4.0 g of BHT three times a day for four weeks. The waitlist-control group participates equally in all clinical trial activities without taking the test drug.

BHT effects is evaluated by changes in the scores of the Korean Version of the Hamilton Depression Rating Scale (K-HDRS), Korean-Beck Depression Inventory-II (K-BDI-II), Korean Symptom Check List 95 (KSCL-95), State-Trait Anxiety Inventory-Korean version (STAI-K), State-Trait Anger Expression Inventory-Korean version (STAXI-K), Insomnia Severity Index (ISI), Instrument on Pattern Identifications for Depression, and EuroQol-5 Dimension (EQ-5D). The scores reflects the improvement in mood and quality of life, using K-HDRS as the primary outcome measure confirmed by changes in the total score of 17 items of K-HDRS observed before and 4 weeks after the trial. This protocol is presented in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 statement (Table 1, Fig. 1).

2. Ethical consideration

The study was approved by the Institutional Review Board (IRB) of Kyung Hee University Korean Medicine Hospital (KOMCIRB 2021-09-008) and complies with the Declaration of Helsinki[15]. Further-

Table 1. Items from the World Health Organization Trial Registration Data Set

Data category	Information
Primary registry and trial identifying number	CRIS, KCT0007272
Date of registration in primary registry	12 May 2022
Source(s) of monetary or material support	Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea
Contact for public/ scientific queries	SC (chosh@khmc.or.kr)
Public title	None
Scientific title	Randomized controlled study to evaluate safety and efficacy of Banhahubak-tang in patients with depression
Countries of recruitment	Republic of Korea
Health condition(s) or problem(s) studied	Major depressive disorder
Intervention(s)	Intervention group: Banhahubak-tang Control group: Waitlist
Key inclusion and exclusion criteria	Inclusion criteria: Male and female adults aged 19 to 65, who are diagnosed with major depressive disorder based on DSM-5, K-HDRS score of 18 or higher and voluntarily participated in the trial Exclusion criteria: K-HDRS score of 27 or higher, risk of suicide, diagnosis of neurological disease and psychiatric diseases
Study type	Type of study: Interventional Study design: randomized; assessor blind; parallel group; treatment Sealed envelopes; computer-generated random numbers
Date of first enrollment	May 2022
Sample size	84
Recruitment status	Not yet recruiting
Primary outcome(s)	K-HDRS
Key secondary outcomes	K-BDI-II, KSCL-95, STAI-K, STAXI-K, ISI, Instrument on Pattern Identifications for Depression, EQ-5D

	Study period			
	Screening	Treatment		Close-out
Visit number	V1	V2	V3	V4
Time point	~-10D	Week 0	Week 4	Week 8
Enrollment:				
Informed consent	X			
Eligibility screen	X	X		
Random allocation		X		
Interventions		◆———	———◆	
Assessments:				
Demographic data	X			
Medical history	X	X		
Vital signs	X	X	X	X
Laboratory test	X		X	X
K-HDRS	X		X	X
The instrument on pattern identifications for depression		X	X	X
K-BDI-II		X	X	X
KSCL-95		X	X	X
ISI		X	X	X
K-BDI-II		X	X	X
STAI-K		X	X	X
STAXI-K		X	X	X
EQ-5D		X	X	X
C-SSRS		X	X	X
Adverse events		X	X	X

Fig. 1. Standard Protocol Items: Recommendations for Interventional Trials Statement (SPIRIT). Overview of study process and outcome assessment. C-SSRS: Columbia-Suicide severity rating scale, EQ-5D: EuroQol-5 Dimension, ISI: Insomnia Severity Index, K-BDI-II: Korean-Beck Depression Inventory-II, K-HDRS: Korean Version of the Hamilton Depression Rating Scale, KSCL-95: Korean Symptom Check List 95, STAI-K: State-Trait Anxiety Inventory-Korean version, STAXI-K: State-Trait Anger Expression Inventory-Korean version.

more, written informed consent will be is made in writing before the participants are included in the trial.

3. Recruitment

Recruitment posters approved by the IRB will be displayed at the hospital to recruit the participants. Further, candidates will be recruited through advertisements in subways and buses, posting documents on bulletin boards of hospitals, online recruitment media, and other appropriate locations. A total of 84 qualified participants will be recruited: 42 at Kyung Hee University Korean Medicine Hospital and 42 at Daejeon University Korean Medicine Hospital. The trial schedules are presented in Fig. 1. A flowchart of the study is presented in Fig. 2.

4. Inclusion criteria

The prospective patients have to meet the following criteria.

1) K-HDRS score of 18 or higher.

2) Men and women aged 19~65 years.

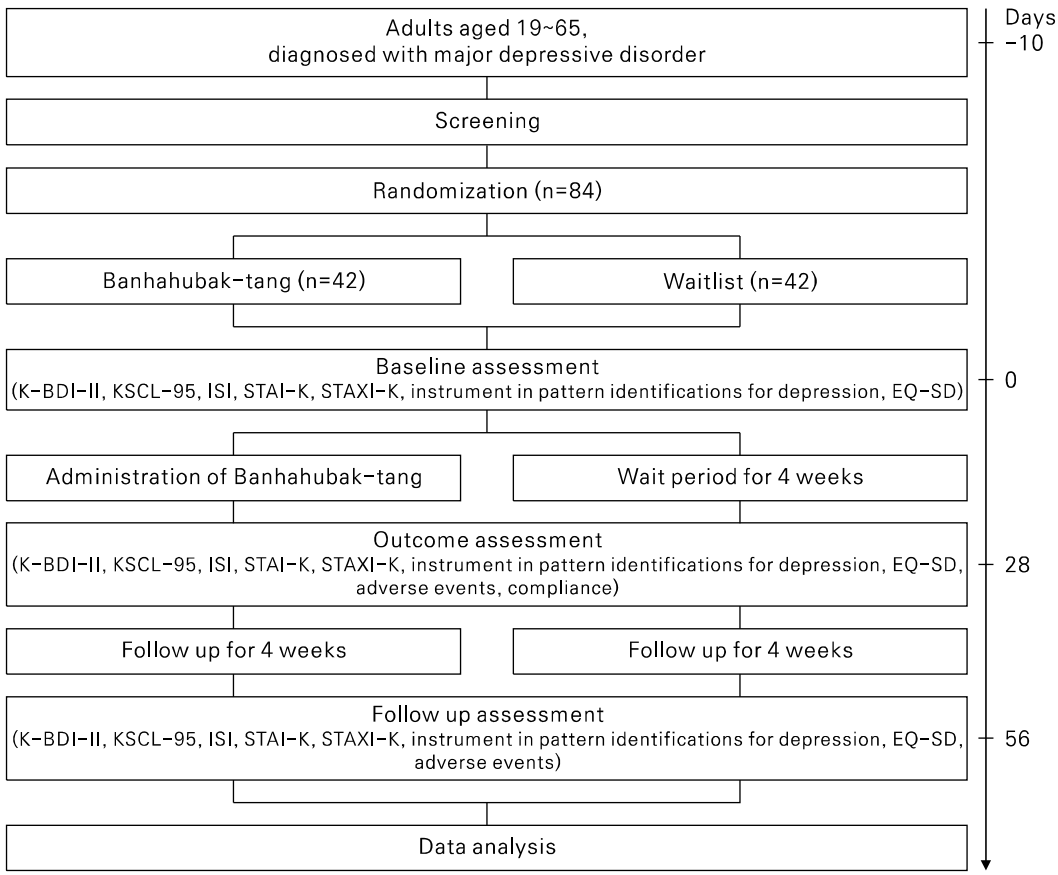

Fig. 2. Flow diagram of participant recruitment.
EQ-5D: EuroQol-5 Dimension, ISI: Insomnia Severity Index, K-BDI-II: Korean-Beck Depression Inventory-II, K-HDRS: Korean Version of the Hamilton Depression Rating Scale, KSCL-95: Korean Symptom Check List 95, STAI-K: State-Trait Anxiety Inventory-Korean version, STAXI-K: State-Trait Anger Expression Inventory-Korean version.

3) Voluntarily deciding to participate and sign the consent form.

4) Patients diagnosed with major depressive disorder according to the DSM-5.

5. Exclusion criteria

The patients with the following criteria were excluded from the trial.

1) A person at risk of suicide.

2) K-HDRS score of 27 or higher.

3) Patients with a major depressive disorder who needed inpatient treatment.

4) Patients who received electroconvulsive therapy (ECT), vagus nerve stimulation (VNS), deep brain stimulation (DBS), light therapy, transdermal magnetic stimulation, and psychotherapy within the last three months.

5) A person diagnosed with and treated for panic disorder, obsessive-compulsive disorder, post-traumatic stress disorder, antisocial personality disorder, borderline personality disorder, histrionic personality disorder, or other severe personality disorders (paranoid, schizoid, narcissistic, avoidant, dependent personality disorder, etc.).

6) History of manic, hypomanic, and mixed episodes.

7) A person who abused, was dependent or had a history of misuse of alcohol or other substances.

8) A person being administered a substance or

drug that may affect the degree of depression (cases when substances such as anxiolytics, antidepressants, antipsychotics, adrenal cortical hormone drugs, estrogen and progestin drugs, L-dopa, digitalis, bromide, cyclosporin, disulfiram, isoniazid, yohimbine, etc. are administered alone or in combination (combination therapy)).

9) A person who was prescribed and administered a thrombolytic or blood coagulation inhibitor.

10) Medical conditions that could affect the degree of depression (e.g., myocardial infarction, arrhythmia, brain tumor, multiple sclerosis, pancreatic disease, hypothyroidism, hyperparathyroidism, Addison disease, Cushing disease, rheumatoid arthritis, cancer, cerebrovascular disease, dementia, etc.).

11) Patients with chronic diseases that are not well controlled even with appropriate treatment (chronic active hepatitis, high blood pressure, diabetes, etc.)

12) A person treated for liver cancer, cirrhosis, chronic renal failure, or congestive heart failure, classified as NYHA Class III～IV.

13) Patients (AST, ALT, ALP≥normal upper limit more than double when screening or creatinine ＞2.0 mg/dL) with renal or liver dysfunction.

14) A person with a genetic problem such as galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption.

15) Diseases that could affect drug absorption or digestion after surgery related to those with disabilities.

16) Persons who participated in other clinical trials within one month before the study started.

17) Hypersensitivity to drugs similar to study intervention and allergic history.

18) A person taking herbal medicines other than the clinical trial drug.

19) Those who did not understand the consent form or had difficulty continuing the trial because of mental retardation or intellectual problems.

20) Pregnant or lactating women.

21) A woman likely to get pregnant and refuses the use of contraceptives (dual contraceptive methods*, intrauterine device, and spermicide) during the clinical trial period.

*dual contraceptive methods : Refer to a case in which barrier method of contraception (condom, diaphragm, etc.) and other contraceptive methods (sterilization, intrauterine device, etc.) are used together.

22) Cases where the examiner determined that it was inappropriate to participate in the clinical trial for other reasons.

6. Randomization and blinding

In the present study, 84 participants who complain of depression are randomized into the intervention or waitlist-control group in a 1:1 ratio after obtaining informed consent. Block randomization is applied for participants who meet the inclusion and exclusion criteria. An independent statistical expert generates the randomization number. The number is placed in a lightproof, sealed envelope and kept in a locked chamber. As this trial is designed as a waitlist-controlled trial, blindfolding of the participants is not applied due to the nature of parallel-design studies. The outcome assessors is blinded and not aware of the intervention received by the participants.

7. Intervention

One 4.0 g packet of BHT granules is administered three times a day for four weeks to the intervention group. The participants' symptoms are evaluated using the K-HDRS, K-BDI-II, KSCL-95, STAI-K, STAXI-K, ISI, Instrument on Pattern Identifications for Depression, and EQ-5D to confirm the effectiveness of BHT in major depressive disorders. Information on the clinical trial drugs is presented in Table 2. The participants in the waitlist-control group participates equally in all scheduled activities of the clinical trial without taking the test drug. For participants in the

Table 2. Information on Clinical Trial Drugs

Name of the product	Banhoo granule
The shape and appearance of the product	Light brown granules
Ingredients and content	Banhahubak-tang X-granules 4.0 g (Banhahubak-tang Soft Ext. 933 mg)
Indication/efficacy	Major depressive disorder
How to store	Confidential container, room temperature storage
Expiration date	36 months from the date of manufacture
Numbering	The manufacturer prepares the test drug according to the random allocation number. The test drug will be labeled in the form of BHT_AA-R-ZZ. The labeled test drug will be provided to the research manager, and willbe managed by the research pharmacist. Where AA stands for institution number, R stands for random assignment, and ZZZ begins with 001 in the order of the subjects to be assigned.
Manufacturer	HANPOONG PHARM & FOODS Co.,Ltd

waitlist-control group, the same drug dose and quantity as in the intervention group are prescribed during the follow-up visit if the participant so wished.

In both the intervention and waitlist-control groups, only participants in the intervention group take the drug and conduct follow-up visits four weeks later to check for changes in symptoms and adverse events. The schedules pertaining to the intervention and waitlist-control groups are shown in Fig. 1 and 2, respectively. The reasons for patient dropouts or withdrawals will be recorded in a case report form. If the participant drops out or withdraw, the date, time, and reason will be recorded in the termination report. The clinical trial-related records and source documents will be transferred to the archive facility of the the institution for three years after completion of the study.

8. Outcome measures

1) Primary outcome mearure

In the present study, the change in the total score of 17 questions on the Korean version of the Hamilton Depression Rating Scale (K-HDRS) after four weeks isthe main outcome[16]. Scores ranging from 0 to 52 are recorded. The higher the score, the more serious is the depression. According to a previous study[17], 0~6 points were considered normal, 7~17 points a mild depression, 18~24 points a moderate depression, and more than 24 points a severe depression. A K-HDRS score of ≥18 points is used as the inclusion criterion in this study.

2) Secondary outcome measure

The timeline for the evaluation of the secondary outcomes is shown in Fig. 1 and 2.

9. Korean-Beck Depression Inventory-II (K-BDI-II)

K-BDI-II was developed in 1961 and is a widely used tool to evaluate the presence or absence of depression and the severity of symptoms. It consists of 21 questions, covering cognitive, emotional, motivational, and somatic symptom domains of depression[18]. Each question is scored from 0 to 3 points, and the total score ranges from 0 to 63 points. The system has the advantage of recording the cognitive symptoms of depression on a self-report scale. Characteristically, it reduces participants' experience in quantifying their psychological statements by allowing them to respond to specific statements instead of simply scoring and evaluating individual symptoms.

10. Korean-Symptom Check List 95 (KSCL-95)

The KSCL-95 can comprehensively measure major

clinical and psychological symptoms[19]. Questions are divided into nine dimensions: depression, anxiety, somatization, obsessive-compulsive, internal sensitivity, hostility, phobic anxiety, paranoid ideation, and psychoticism. We use the test when excluding participants with symptoms other than depression because it is possible to determine whether they have multiple psychiatric symptoms using the test during the first visit.

11. Insomnia Severity Index (ISI)

It is a test used to evaluate sleep quality and insomnia[20], examining the severity of sleep onset, sleep maintenance, early morning awakening problem, satisfaction with current sleep pattern, interference with daily functioning, noticeability of impairment attributed to the sleep problem, and level of distress caused by the sleep problem. A total score of 8 points or more indicates insomnia. In addition, we use the test to determine the presence and severity of sleep discomfort, commonly accompanied by depression.

12. State-Trait Anxiety Inventory-Korean version (STAI-K)

STAI-K, developed by Spielberger et al.[21], simultaneously measures state and trait anxiety. Originally developed as a tool to evaluate anxiety symptoms in normal adults, it is also useful for measuring anxiety in psychiatric patients. We use the test to evaluate anxiety symptoms, the main comorbid symptoms of depression. Evaluating anxiety consists of state anxiety (20 questions) and trait anxiety (20 questions). Each question is evaluated on a four-point scale, with 1='not at all/almost never', 2='somewhat/sometimes', 3='moderately so/often', and 4='very much so/almost always'.

13. State-Trait Anger Expression Inventory-Korean version (STAXI-K)

The STAXI-K test consists of state anger (10 questions) and trait anger (10 questions) to measure anger experience. It is also designed to measure anger suppression (8 questions), anger expression (8 questions), and anger control (8 questions), respectively[22]. We evaluate anger symptoms using STAXI-K. Each question is scored on a four-point scale: 1 'almost never,' 2 'sometimes,' 3 'often,' 4 'almost always' on the anger-expression scale, and 1 'not at all,' 2 'somewhat,' 3 'moderately so,' 4 'very much so' on the state-trait anger scales.

14. An instrument on pattern identifications for depression

This is a structured interview tool for depression developed by a group of experts composed of Korean medicine neuropsychiatric professors and is under evaluation for reliability and validity[23]. There are six types of instruments for pattern identification for depression: Stagnation of Liver Gi, Dual Deficiency of the Heart and Spleen, Relieving Stagnation of Phlegm-Gi, Gi deficiency Mingled with Sputum, Stagnant Gi transforming into Fire, and Yin deficiency with effulgent fire. Using the structured interview tool, the scores of the six types of dialectic can be calculated, and dialectic trends can be identified. When this pattern identification tool is used along with the existing tool for evaluating depression, it has the advantage of being able to diagnose the symptoms of depression in Korean medicine systematically.

15. Health-Related Quality of Life (EQ-5D)

The EQ-5D is a tool for measuring general health status developed by the EuroQol group[24]. It consists of questions about five items and questions about overall health status and is quick and straightforward

to use. In addition, the EQ-5D is a quality of life evaluation tool that has been objectively and reliably verified for Koreans. We adopted this objective tool to measure participants' quality of life.

16. Adverse events

The research manager or research doctor observes whether there are adverse events presented by participants in the clinical trial. Participants are examined at each visit, and the causal relationship with the test treatment is recorded in the "adverse event report." The expected adverse events of the drugs (symptoms, start date, duration, etc.) were recorded. The degree of adverse events was evaluated step by step by referring to the evaluation criteria (mild, moderate, and severe). The test manager evaluates the causal relationship with the test drug by classifying it into six stages of being related (Definitely related, Probably related, Possibly related, Probably not related, Definitely not related and Unknown) according to the evaluation criteria.

17. Safety

The participants' safety is evaluated using vital signs and laboratory tests. Adverse events and their association with drug administration will be also evaluated. The results are recorded for every participant registered in the clinical trial who had taken clinical trial drugs more than once. An adverse event refers to any harmful and unintended sign, symptom, or disease that has occurred in test subjects who have been administered clinical trial drugs. Intergroup comparison of the number (or ratio) of occurrence of adverse events associated with treatment is performed using Pearson's chi-square test or Fisher's exact test.

In addition, the participant will be excluded from the study in the following cases.

1) In case the participant violates the inclusion criteria or meets exclusion criteria.

2) In case the parcitiapnt has a serious adverse events or the participant refuse to participate in the trial due to adverse events.

3) In case a systemic disease that was not identified in the screening visit is found.

4) In case a parcitipant or legal representative withdraws consent to participate in the clinical trial.

5) In case of significantly low compliance to the trial.

6) In case the investigator determines that the participant needs other treatment due to worsening symptoms.

7) In case the participant is lost to follow up.

8) In case the participant takes drugs which may affect the result of the trial without the investigator's instruction or consent during the trial period.

9) In case the investigator judge that it is inappropriate to continue the trial.

18. Statistical methods

1) Sample size calculation

The sample size calculation was performed based on the independent sample t-test for the difference between the two groups (intervention group vs. waitlist-control group) in the total score change of the 17 K-HDRS questions observed before the start of the test (baseline) and at the end of the 4-week administration period[25]. The average difference between the HAM-D17 question total score changes in the intervention and waitlist-control groups was considered to be 4.0 points based on a previous study that evaluated the efficacy of herbal medicine in depression[25]. The standard deviation of the total point change in the two groups was assumed to be 5.78. The significance level (α) was set to 5%, and the statistical power ($1-\beta$) was set to 80%. The allocation ratio between the groups was 1:1. The expected drop-

out rate was assumed to be 20%. The number of participants (n) required per group was calculated as follows.

$N=[2(Z_{\alpha/2}+A_{\beta})^2\sigma^2]/d^2(1-r)=[2(1.96+0.84)^2(5.78)^2]/(4)^2(1-0.2)\approx 42$

2) Statistical analysis

All statistical analyses are performed using a two-sided test; the significance level is set at 5%. The R statistical program (R Core Team, 2021) is used. The main analysis group is the Full Analysis Set (FAS) group. The per-protocol (PP) analysis is performed using participants who completes the test. Participants who violate the clinical trial plan after the start of the trial are excluded from the analysis. The efficacy evaluation is based on the FAS analysis, and the PP analysis is performed as a supplement. To comply with this study, the overall compliance must be at least 75% during the treatment period. If the compliance is less than 75%, the participants are considered to have low compliance and excluded from the PP analysis group.

Compliance (%)=Actual number of medications taken/Number of medications to be administered * 100

III. DISCUSSION

This study will assess the efficacy and safety of BHT in treating depression compared to the waitlist-control group. Depression is a common psychiatric disorder that can cause multiple symptoms and decrease life satisfaction. Although there is much experimental evidence available about BHT, and it is currently used to treat depression in Korean clinics, there have been few clinical trials. The results of this study provide new information about the efficacy and safety of BHT treatment of depression.

As depression has a variety of symptoms, we evaluate the effects of BHT on patients with depression in various ways. The K-HDRS and K-BDI-II are selected to evaluate depression. Insomnia is assessed using the ISI, and the degree of anxiety and anger are measured using the STAI-K and STAXI-K. Quality of life is evaluated using the EQ-5D, and overall psychotic features are assessed using the KSCL-95.

In summary, there is a continuous demand for new antidepressants with fewer side effects and better efficacy. BHT has been commonly used in clinical practice, but it lacks clinical evidence to support its use. This randomized controlled trial provides high-quality clinical evidence of the efficacy and safety of BHT in treating depression.

TRIAL STATUS

The study is registered with the Clinical Research Information Service (CRIS) (KCT0007272). This protocol is based on version 1.3 of 03 Jan 2022. First participant will be enrolled in May, 2022. We anticipate that the recruitment will be completed by December, 2023. The data set is summarized in Table 1.

DECLARATIONS

The Institutional Review Boards of Kyung Hee University Korean Medicine Hospital approved the study (KOMCIRB 2021-09-008). Written informed consent to participate will be obtained from all participants.

CONFLICT OF INTEREST DECLARATION

The authors declare that they have no competing interests.

FUNDING

None.

AUTHORS' CONTRIBUTIONS

SC is the chief investigator who conceived the study and led the proposal and protocol development. SC, SL, YK and DK contributed to the study proposal and overall design. YK and SL developed the protocol. All authors read and approved the final manuscript.

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